PB88-107800

Health and Environmental Effects Profile for Chloropropenes

(U.S.) Environmental Protection Agency
Cincinnati, OH

May 83

U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-107800

EPA/600/X-84/119
MAY 1983

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CHLOROPROPENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/X-84/119		PB88-107800

4. TITLE AND SUBTITLE	5. REPORT DATE
Health and Environmental Effects Profile For Chloropropenes	May 1983
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Health and Environmental Effects Profile for Chloropropenes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chloropropenes have been determined to be systemic toxicants. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 3-Chloropropene is 1.6×10^{-3}, 1,2,3-Trichloropropene is 4.6×10^{-3} for oral exporsure. Existing data are insufficient to determine for the other isomers.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Public	Unclassified	50
	20. SECURITY CLASS *(This page)*	22. PRICE
	Unclassified	A03 11.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, D.C.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

TABLE OF CONTENTS

		Page
	EXECUTIVE SUMMARY	vi
1.	INTRODUCTION	-1-
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	-4-
3.	EXPOSURE	-8-
4.	PHARMACOKINETICS	-9-
5.	EFFECTS	-11-
6.	AQUATIC TOXICITY	-25-
7.	EXISTING GUIDELINES AND STANDARDS	-28-
8.	APPROACHES TO RISK ASSESSMENT	-29-
9.	REFERENCES	-31-

EXECUTIVE SUMMARY

The four chloropropenes reviewed in this profile [3-chloropropene (allyl chloride), 1,2,3-trichloropropene, 1,1,2,3-tetrachloropropene and 1,1,2,3,3-pentachloropropene] are liquid at room temperature. 3-Chloropropene is a highly volatile liquid and is soluble in water. The United States production of 3-chloropropene in 1973 was 300 million pounds. It has been estimated that ~4.4 million pounds of this compound are lost annually during its manufacture. Both 1,1,2,3-tetrachloropropene and 1,1,2,3,3-pentachloropropene have been detected in pulp and paper mill effluents and are probably produced during the chlorination of pulps.

The most likely fate-determining reaction of 3-chloropropene in the atmosphere is its interaction with ozone (O_3). The half-life of the O_3 reaction with 3-chloropropene has been estimated to be 2 hours. From the few available studies, it can be concluded that evaporation from water is one of the most important transport processes for 3-chloropropene present in aqueous phases. It has been estimated that 1,2,3-trichloropropene evaporates from the aqueous phase with a half-life of 45 minutes.

No quantitative monitoring data that would permit estimation of human intake from air, water, foods and skin exposure are available for any of the four chloropropenes.

Only limited information is available on the toxicity of 1,2,3-trichloropropene, 1,1,2,3-tetrachloropropene and 1,1,2,3,3-pentachloropropene. A chronic toxicity study in rats, hamsters and dogs indicates that 1,2,3-trichloropropene may be injurious to the liver following inhalation; however, a full report of this study is not available. Mutagenicity studies of all four chloropropenes, using the Ames assay as well as other test systems, have been positive both with and without the addition of a mammalian meta-

bolic activation system. The toxicologic information is more complete for 3-chloropropene. Subchronic studies in animals indicate adverse effects in the liver, kidney and lungs following inhalation at an exposure level of 8 ppm for 1 month. There is some support for these conclusions from observations of workers exposed to 3-chloropropene. Mutagenicity assays with 3-chloropropene in the Ames system show a strong positive when vapor exposure is used; however, the purity of the compound is not stated. Other mutagenicity assays indicate a smaller but still positive response. An NCI (1978) bioassay of 3-chloropropene concluded that there was suggestive evidence of carcinogenicity, since some tumor types are unique to the treated animals, although not statistically greater than the control values. Evidence for teratogenicity is conflicting, with one preliminary study indicating that 3-chloropropene is both teratogenic and fetotoxic, while a second study (reported only in abstract form and using a different route of administration) concludes the opposite. Until further studies are available, a criteria for 3-chloropropene has to be derived from the TLV which is based on subchronic toxicity data, and, using this data, an ADI of 110 µg/day can be calculated. An ADI is also estimated for 1,2,3-trichloropropene of 320 µg/day.

Limited information was found on the aquatic toxicity of 3-chloropropene. Acute mortality assays with four species of freshwater fish under static conditions show that 24- to 96-hour LC_{50} values range from ~20-25 mg/ℓ (fathead minnows, goldfish) to 40-60 mg/ℓ (bluegill sunfish, guppies). Inhibition of cell multiplication occurs in protozoans (8.4 mg/ℓ x 72 hours, >240 mg/ℓ x 20 hours), algae (6.3-8.2 mg/ℓ x 8 days) and a bacterium (115 mg/ℓ x 16 hours).

1. INTRODUCTION

Available data on the physical properties, sources, production and use of 3-chloropropene, 1,2,3-trichloropropene, 1,1,2,3-tetrachloropropene and 1,1,2,3,3-pentachloropropene are summarized below.

3-Chloropropene (allyl chloride) is a colorless liquid at ambient temperature (Weast, 1980). The compound is manufactured by chlorination of propylene (NIOSH, 1976). 3-Chloropropene enters the environment during the manufacture and usage of the compound (NIOSH, 1976). Some physical parameters are:

CAS registry number:	107-05-1
Formula:	$ClCH_2CH = CH_2$
Molecular weight:	76.53
Melting point:	-134.5°C (Weast, 1980)
Boiling point:	45°C (Weast, 1980)
Density:	0.9376 (g/mℓ) at 20°C (Weast, 1980)
Flash point:	-28.9°C, open cup; -31.7°, closed cup (Torkelson and Rowe, 1981)
Vapor pressure at 25°C:	368 mm of mercury (Torkelson and Rowe, 1981)
Solubility in water:	3.6 g/ℓ at 20°C (Torkelson and Rowe, 1981)
Production:	Produced in the United States by Dow Chemical Co. and Shell Chemical Co. (SRI, 1981). The United States production in 1973 was 300 million pounds (NIOSH, 1976).

3-Chloropropene is used in the manufacture of allyl alcohol; as thermosetting resins for varnishes, plastics and adhesives; and in the synthesis of pharmaceuticals, glycerols and insecticides (Hawley, 1971).

Pertinent data regarding production and sources of 1,2,3-trichloropropene were not located in the available literature. Some physical parameters are:

CAS registry number:	96-19-5
Formula:	CH_2Cl-CCl=$CHCl$
Molecular weight:	145.42
Boiling point:	142°C (Weast, 1980)
Density:	1.414 (Weast, 1980)
Solubility in water:	~4300 mg/ℓ at 25°C (Mabey et al., 1982)
Log octanol/water partition coefficient:	~2.07 (Mabey et al., 1982)

A mixture of trichloropropenes has satisfactory nematicidal and antiphylloxeral effects (Melnikov, 1971).

1,1,2,3-Tetrachloropropene can enter the environment as a result of chlorination of pulp; this compound has been reported at a concentration of 100 mg/ton in pulp and paper mill effluents (CPAR, 1978). Some physical parameters are:

CAS registry number:	10436-39-2
Formula:	CH_2Cl-CCl=CCl_2
Molecular weight:	179.86
Boiling point:	of 1,2,3,3-isomer: 165°C (Weast, 1980)
Density:	of 1,2,3,3-isomer: 1.537 (Weast, 1980)

1,1,2,3,3-Pentachloropropene is also formed from the chlorination of pulp, and has been detected in pulp and paper mill effluents at a concentration of 100 mg/ton pulp (CPAR, 1978). Some physical parameters are:

CAS registry number:	1600-37-9
Formula:	$CHCl_2$-CCl = CCl_2
Molecular weight:	214.31
Boiling point:	185°C (Weast, 1980)
Density:	1.632 (Weast, 1980)

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Brown et al. (1975) reported that 3-chloropropene was unreactive towards RO_2• radicals in the atmosphere. It reacted with OH• radicals in the atmosphere (with a half-life of ~21 hours) resulting in the formation of 2-chloroacetaldehyde. The reaction of O_3 with 3-chloropropene was faster and had a half-life of 9 hours; the products of this reaction were formaldehyde and 2-chloroacetaldehyde.

Sears (1973) investigated the photolytic reactions of 3-chloropropene at different wavelengths and found that 1,5-hexadiene and 5-chloro-4-chloromethyl pentene were the major reaction products at 27°C and at a wavelength of 300 nm. The quantum yields of the two product formations were 0.23 moles/einstein and 0.25 moles/einstein, respectively. Therefore, photolysis may play some role in determining the fate of this chemical in the troposphere.

Pertinent data regarding the atmospheric fate and transport processes of 1,2,3-trichloropropene, 1,2,3,3-tetrachloropropene or 1,1,2,3,3-pentachloropropene were not located in the available literature.

2.2. WATER

3-Chloropropene hydrolysis in aqueous solution has a half-life of 7 days (Brown et al., 1975). A review of more recent data, however, put the hydrolysis half-life at 69 days for 3-chloropropene at 25°C and pH 7 (Mabey and Mill, 1978). The half-life of 3-chloropropene evaporation from water, depth of 6.5 cm at ~25°C under 200 rpm stirring conditions in still air (<0.2 mph air current), has been determined to be 27 minutes (Dilling, 1977; Dilling et al., 1975). The biodegradability of 3-chloropropene in aqueous solution was studied by Bridie et al. (1979). These authors

found that only 14% of the theoretical oxygen demand was biologically consumed with adapted seeding after 5 days of incubation at 20°C. It appears from the above discussion that evaporation from aqueous phase to air is the primary mode of transport for this chemical.

The half-life of 1,2,3-trichloropropene evaporation from water (1 ppm concentration) with 200 rpm stirring in still air (<0.2 mph air current) at a temperature of ~25°C and a solution depth of 6.5 cm was determined to be 45 minutes (Dilling, 1977).

1,2,3-Trichloropropene is not expected to undergo either photolytic or oxidation (by peroxy radicals and singlet oxygen) reactions in natural aquatic media (Mabey et al., 1982). The hydrolytic fate of this compound in aquatic media can be calculated from the estimated neutral hydrolysis rate constant of 4×10^{-5} hr^{-1}. The calculated hydrolysis half-life of over 720 days indicates that this reaction is not a significant fate determining process. Similarly, the biodegradation half-life for this chemical can be calculated from the estimated microbial degradation rate constant of 10^{-10} $m\ell$ $cell^{-1}$ hr^{-1} (Mabey et al., 1982) and the estimated concentration of microorganisms of 5×10^{5} cells $m\ell^{-1}$ (Burns et al., 1981) in aquatic media. The calculated half-life of ~580 days is indicative that the compound may be persistent towards biodegradation in natural aquatic media.

The sediment sorption partition coefficient for 1,2,3-trichloropropene from aquatic media can be estimated from physical properties of the molecule. The organic carbon partition coefficient (K_{oc}) is first calculated from the octanol-water partition coefficient (K_{ow}) by correlation equations. The sediment sorption partition coefficient is then calculated from K_{oc} by the equation:

$$\text{Sorption partition coefficient} = \frac{K_{oc} \times \% \text{ organic carbon content}}{100\%}$$

Using a value of 2.07 for log K_{ow} (Mabey et al., 1982), log K_{oc} is calculated to be 1.95, 1.98 or 2.50, depending on the correlation equation used (Briggs, 1981; Schwarzenbach and Westall, 1981; Kenaga and Goring, 1980). This log K_{oc} value is close to the experimental log K_{oc} value for benzene (Schwarzenbach and Westall, 1981). Thus, the sorption characteristics of this compound in aquatic media can be expected to be similar to that of benzene. In other words, it may not be significantly sorbed onto sediments containing low oragnic matter, whereas sediments rich in organic matter may show higher sorptive capacity. If a sediment organic content of 0.5% (typical of liver sediment) is assumed, a sediment sorption partition coefficient of ~0.48-1.58 is estimated, indicating a sediment concentration roughly equivalent to the water concentration, under equilibrium conditions.

Pertinent data regarding the fate and transport of 1,2,3,3-tetrachloropropene or 1,1,2,3,3-pentachloropropene in water were not located in the available literature.

2.3. SOIL AND OTHER MEDIA

Experimental data regarding the fate and transport processes of the subject chloropropenes in soil or other media were not located in the available literature. However, the specific fate and transport of 1,2,3-trichloropropene might be predicted from the available physicochemical data. Based on the values of log K_{oc}, solubility and aqueous volatility data, and comparing with the corresponding values for benzene (Callahan et al., 1979), it can be predicted that this compound would have higher volatility and water leaching from soils than benzene. However, no prediction regarding the microbial degradability and chemical oxidizability of this compound in soil can be made at the present time.

2.4. SUMMARY

It should be emphasized that the fate of a chemical predicted from theoretical calculations, may often vary considerably from the experimental data. In the preceding discussions, the fate of 1,2,3-trichloropropene due to a few likely environmental processes has been predicted from theoretical equations only when experimental data were unavailable. However, extreme caution should be exercised in interpreting the predicted fate data based on theoretical calculations alone.

3. EXPOSURE

3.1. WATER

No monitoring data that would permit estimation of exposure from water ingestion for any of the four chloropropenes were located in the available literature.

3.2. FOOD

No monitoring data that would permit estimation of exposure from food ingestion for any of the four chloroprenes were located in the available literature.

3.3. INHALATION

Brown et al. (1975) estimated that 4.4 million pounds of 3-chloropropene are lost annually during the manufacture of this chemical, but no atmospheric monitoring data are available. NIOSH (1976) estimated that ~5000 workers are occupationally exposed to 3-chloropropene in the United States. Kiparisova and Stepanenko (1976) determined a concentration of 0.3 mg/m^3 in the air of industrial facilities. 1,2,3,3-Tetrachloropropene was detected in the air of Houston, Texas, and surrounding vicinity (Pellizzari et al., 1976). Quantitative measurements were not determined.

Pertinent data regarding levels of 1,2,3-trichloropropene or 1,1,2,3,3-pentachloropropene in air were not located in the available literature.

3.4. DERMAL

Pertinent data regarding human dermal exposure to any of the four chloropropenes were not located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of any of the four chloropropenes were not located in the available literature.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of any of the four chloropropenes were not located in the available literature.

4.3. METABOLISM

Kaye et al. (1972) investigated the formation of urinary and biliary metabolites in rats following the subcutaneous injection of 3-chloropropene, 1 mℓ as a 10% v/v solution. Paper chromatography revealed three urinary metabolites identified as allylmercapturic acid, 2- or 3-hydroxypropylmercapturic acid and allylmercapturic acid sulphoxide. Biliary metabolites included allylmercapturic acid, S-allylglutathione and S-allyl-L-cysteine. The authors proposed that 3-chloropropene was metabolized through conjugation with glutathione. Some metabolism was also inferred to occur through the formation of the alcohol, 3-chloropropanol, since this metabolite would result in the formation of 3-hydroxypropylmercapturic acid which was detected in the urine.

Ivanetich et al. (1978) surveyed 50 organic compounds for <u>in vitro</u> interaction with microsomal drug metabolizing enzymes. Type I binding to cytochrome P-450 was demonstrated by difference spectra following incubation of 3-chloropropene with liver microsomal enzymes. In this reaction there was a 47% loss of cytochrome P-450, although there was no loss of the heme moiety (unlike some other chlorinated compounds). Cytochrome b_5 and NADPH-cytochrome C reductase were unaffected by incubation with 3-chloropropene. As indicated by the oxidation of NADPH, there was some metabolism of

the compound in this *in vitro* assay. Patel et al. (1981) reported somewhat conflicting results in which microsomal cytochrome P-450 from the livers of phenobarbital pretreated rats was incubated *in vitro* with 3-chloropropene. In this study there was an observed loss of cytochrome P-450; however, this loss was accompanied by an equal molar loss of the heme moiety. Although both studies indicate that 3-chloropropene destroys cytochrome P-450, it is not clear why different results were obtained on the destruction of the heme moiety.

Pertinent data regarding the metabolism of the other chloropropenes were not located in the available literature.

4.4. EXCRETION

Pertinent data regarding the excretion of any of the four chloropropenes, except the urinary metablolites discussed in Section 4.3. for 3-chloropropene, were not located in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

The National Cancer Institute (NCI, 1978) has conducted a bioassay in Osborne-Mendel rats and B6C3F1 mice to determine the possible carcinogenicity of 3-chloropropene. The results of this assay also appear in a review on halogenated hydrocarbons by Weisburger (1977). Groups of 50 animals of each sex were administered 3-chloropropene in corn oil by gastric intubation, 5 days/week for 78 weeks, followed by observation periods of 30-33 weeks (rats) and 14 weeks (mice). The initial doses given to rats were 70 and 140 mg/dose and 55 and 110 mg/dose for the low and high dose male and female groups, respectively. However, as a result of toxicity, the doses were changed during the study, with the final time-weighted average doses being 57 and 77 mg/dose and 55 and 73 mg/dose, respectively, for the low and high dose male and female rats. Similarly, the initial dose given to mice was changed during the study, with the final time-weighted average dose being 172 and 199 mg/dose and 129 and 258 mg/dose, respectively, for the low and high dose male and female mice. The 3-chloropropene used in this study was ~98% pure.

Treatment-related mortality was high in the high dose male mice and high dose male and female rats, with sufficient numbers of animals (in these two groups) dying early to preclude an adequate evaluation of a carcinogenic response. In rats of both sexes there was no statistically significant increase in the incidence of any tumor type. Similarly, no statistically significant increase in tumor incidence was observed in mice, but four squamous-cell carcinomas of the forestomach in the low dose male and female mice and four squamous-cell papillomas of the stomach in the low and high

dose female mice were observed. Although these tumors were not significantly increased over the vehicle controls (no observed tumors), the rarity of this tumor type in historical controls resulted in the authors concluding that there was suggestive evidence that 3-chloropropene produced a carcinogenic response in mice.

Theiss et al. (1979) and Van Duuren et al. (1979) investigated the carcinogenic potential of 3-chloropropene in surveys of organohalides. Theiss et al. (1979) used the strain A mouse bioassay where 10 male and 10 female animals received intraperitoneal injections of 3-chloropropene 3 times/week for 8 weeks. The compound was tested at three dose levels consisting of the maximum tolerated dose, 3.20 mmol/kg (243 mg/kg), and lower doses of 1.60 mmol/kg (122 mg/kg) and 0.64 mmol/kg (49 mg/kg). Only the high dose group had a suggestive positive response, with a significant increase ($P<0.05$) in the number of adenomas per lung demonstrated by either the T test or the X^2 test, but not by both tests; it was not indicated which test revealed the significant difference. It was concluded that 3-chloropropane was a borderline tumorigen. In the study by Van Duuren et al. (1979), groups of 30 Ha:ICR female mice were exposed to 3-chloropropene at a dose of 94 mg/application on the skin applied 3 times/week for life. In a similar experiment, mice were treated with 3-chloropropene followed by promotion with phorbol myristate acetate, while an additional group of 30 female mice received weekly subcutaneous injections of 1.5 mg of 3-chloropropene. No increase in skin papillomas or injection site sarcomas were observed. There was evidence in this latter study that 3-chloropropene was a tumor initiating agent, but the compound did not act as a complete carcinogen.

The data from the three carcinogenicity studies provide insufficient evidence to conclude that 3-chloropropene is carcinogenic in experimental animals.

5.2. MUTAGENICITY

Mutagenicity bioassays of some of the chloropropenes have been conducted using a number of *in vitro* test systems. Little success was achieved with initial assays of 3-chloropropene in the standard plate incorporation Ames assay. De Lorenzo et al. (1977) reported that 3-chloropropene was negative in the Ames assay, although the *Salmonella typhimurium* specific tester strains and use of a metabolic activation system were not clearly designated. Using the same plate incorporation assay, Bignami et al. (1980) reported that 3-chloropropene was mutagenic both with and without metabolic activation in strain TA1535. The revertant numbers for TA1535 were 16 and 16 for controls compared with 25 and 63 for the highest dose group in the presence and absence of S-9, respectively. A dose response relationship was evident in strain TA1535. Results were marginal or negative for TA100 using the plate incorporation assay. Bignami et al. (1980) also performed a spot test using both tester strains; results were both positive and dose related for TA1535 and marginal for TA100. Dose-related positive responses were also observed in *S. coelicolor* for forward and back mutations (streptomycin resistance and histidine independence, respectively), in both the plate and spot test. In testing conducted with *A. nidulans*, however, a negative response was reported for the plate test experiments. Based on the reported lack of toxicity these results might be judged as inconclusive. The spot test was also reported to be negative, but a 2-fold increase in Su-meth forward mutations could indicate a marginal response.

In order to overcome the problem of volatilization, Simmon (1978) placed petri dishes containing the tester strains in a desiccator containing vapors of 3-chloropropene (purity not mentioned). A dose related increase in revertants of strain TA100 was observed following incubation of the bacteria at 37°C for 8 hours in desiccators containing 0.1-0.5 mℓ of 3-chloropropene. Mutagenic activity was present both in the presence and absence of a liver metabolic activation system prepared from Aroclor pretreated rats. The mutagenic response (~180 revertants in the controls, compared with 1980 in the plates exposed to 0.5 mℓ of test compound) was greater in the presence of S-9 (without S-9 the revertant number was ~1350).

McCoy et al. (1978) reported that 3-chloropropene was also mutagenic to strains TA100 and TA1535 in a modified vapor exposure assay in which the petri dish, containing the compound on a filter disc, was placed in a sealed plastic bag prior to incubation. The data presented, however, showed that only strain TA1535 in the presence of an S-9 activation system had a doubling of revertants in the treated plates (73 revertants) compared to controls (10 revertants). In the presence of the activiation system there was a dose response relationship between 0, 1 and 10 µℓ/plate. No mutagenic activity was observed in strain TA1538. Positive results were also noted for the yeast Saccharomyces cerevisial using a modified procedure which placed agar plates in plastic bags.

An increase in revertants (TA1535) was also observed by Biles et al. (1978) using a dessicator technique at doses of 10 and 50 µℓ without activation. A dose of 100 µℓ was reported toxic.

In studies of structure activity relationships, Eder et al. (1980) and Neudecker et al. (1980) tested 3-chloropropene for mutagenic activity in a liquid suspension assay using S. typhimurium strain TA100. In this test

system the compound and bacteria were incubated in liquid media in a tightly capped tube for 90 minutes at 37°C prior to plating. According to the Eder et al. (1980), 3-chloropropene was purified by preparative gas chromatography to 100% purity. Using this test system, 3-chloropropene was mutagenic in the absence of metabolic activation; revertant numbers increased from ~200 for control plates to 500 for plates incubated with 15 µmol/mℓ of test compound. Negative results were obtained in the presence of a metabolic activation system. In the testing by Neudecker et al. (1980) TA100 was exposed to doses of 100% pure 3-chloropropene up to 15 µmoles/2 mℓ. There were 100 spontaneous revertants both with and without metabolic activation. About 100 revertants were also noted at the high dose in testing performed with metabolic activation. Approximately 250 revertants were noted without metabolic activation.

The available data lead one to conclude that commercial 3-chloropropene is a direct-acting matagen in the bacteria S. typhimurium and Streptomcyes coelicolor and the yeast Saccharomyces cerevisiae and that purified material is directly mutagenic in S. typhimurium. Differing responses obtained with 3-chloropropene with and without metabolic activation may be due to contaminants in the different samples tested. For example, the purity of the substance tested by Simmon was unknown and this may explain the differing results between his lab and that of Eder and Neudecker. [In this context it should be noted that Bignami et al. (1980) observed stronger mutagenic responses with S-9 than without.] More importantly, differing results between the labs may also be due to other variables such as the different sources of S-9 mix used. Eder and Neudecker used S-9 mix from Wistar rats and NMRI mice while Bignami et al. and Simmon used S-9 mix from Sprague-Dawley rats.

In studies of chlorinated products of paper pulp mill effluent, 1,1,2,3-tetrachloropropene was tested for mutagenicity in the standard plate incorporation assay using Salmonella strains TA1535, TA100, TA1537, TA1538 and TA98 (Nestmann et al., 1980). A dose response increase in revertants was observed in strains TA1535, TA100 and TA98; TA98 was the most sensitive, with 2610 revertants in the absence of S-9 at a dose of 250 µg/plate. Activity was also observed in the presence of S-9 although to a lesser degree. Using another assay system, Ellenton et al. (1981) observed mutagenic activity in the fluctuation test with S. typhimurium TA1535, but not with E. coli WP2. In mammalian cell culture 1,1,2,3-tetrachloropropene produced chromosomal aberrations in Chinese hamster ovary (CHO) cells in the absence of metabolic activation, as well as an increase in sister chromatid exchange. The addition of S-9 increased the chromosomal aberrations ~10-fold; the frequency of sister chromatid exchange decreased. Also, 1,1,2,3-tetrachloropropene caused DNA damage in CHO cells as indicated by altered sedimentation patterns in alkaline sucrose gradients. These studies clearly indicate that 1,1,2,3-tetrachloropropene is mutagenic and can directly interact with mammalian DNA.

Nestmann et al. (1980), in their investigation of pulp mill effluent components, also tested 1,1,2,3,3-pentachloropropene for mutagenic activity in S. typhimurium strain TA100. This compound showed a dose dependent increase in revertant colonies in the absence of S-9 with a maximum of ~800 colonies at 150 µg/plate. Activity was less in the presence of S-9, with the maximum reversion rate only about double control values. Similar results were obtained with 1,2,3-trichloropropene in strain TA100 (Stolzenberg and Hine, 1980), with greater activity (4524 revertants/10 µmol) in the absence of S-9 than in the presence of S-9 (1225 revertants/

10 μmol). The more highly chlorinated chloropropenes appear to be strong mutagens in the Ames assay.

5.3. TERATOGENICITY

Hardin et al. (1981) performed preliminary tests for teratogenicity on a number of workplace chemicals including 3-chloropropene. A group of 10-15 pregnant Sprague-Dawley rats received intraperitoneal injections of 3-chloropropene at a dose of 80 mg/kg on days 1 through 15 of gestation. This dose was determined to be the maximum tolerated dose. On day 21 of gestation, the animals were sacrificed and the fetuses examined for visible signs of external and internal abnormalities. Treatment related maternal toxicity was observed as indicated by increased weight of the heart, liver, spleen and kidney, while fetal toxicity was indicated by an increased incidence of resorption. Skeletal malformations were not present in the fetuses, but there was a statistically significant increase in edema and short snout with protruding tongue. These preliminary results indicate that 3-chloropropene produced both maternal and fetal toxicity and also increased the incidence of some fetal malformations.

John et al. (1980) reported that the inhalation of 3-chloropropene at levels of 0, 30 or 300 ppm did not elicit a teratogenic response in pregnant Sprague-Dawley rats or New Zealand rabbits. The rats and rabbits were exposed 7 hours/day on days 6 through 15 or 18 of gestation, respectively. The only effect of treatment was a slight increase in fetal toxicity in rats exposed to 300 ppm of the compound. The conflicting results in this study with those of Hardin et al. (1981) may reflect the different routes of administration, the different lengths of exposure or the different doses administered.

Pertinent data regarding the teratogenicity of the other chloropropenes were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of the four chloropropenes were not located in the available literature, except for the fetal toxicity reported in studies on the teratogenicity of 3-chloropropene.

5.5. CHRONIC TOXICITY

NIOSH (1976) reported on a German epidemiology study by Hausler and Lenich (1968) of 45 men and 15 women employed in a 3-chloropropene manufacturing plant. These workers, depending on their specific jobs, were exposed to measured levels of 3-chloropropene between 1 and 113 ppm. Urinalysis revealed two individuals with traces of protein, a few erythrocytes, epithelial cells and leukocytes, and five individuals with slightly increased urobilinogen levels. Also, liver tests indicated early signs of damage. These results were considered only suggestive of kidney and liver injury, since pre-exposure values were not available. Following design changes in the plant which reduced exposure to between <1 and 36 ppm, abnormal values for the liver test returned to the normal range within 6 months, although the data for this conclusion were not presented.

Several Russian studies have investigated the health of workers exposed to 3-chloropropene; however, these studies were only available in abstract form, and the validity of the conclusions cannot be determined. Both kidney (Ali-Zade, 1979) and liver (Alekperov et al., 1980) changes were observed in exposed workers (the exact changes were not mentioned), but these workers were exposed additionally to the vapors of mercury and propylene in the respective reports. Aleskerov (1977, 1979a,b) reported dose related changes in EKG patterns, maximum ventriculation rate, and other disorders of the

cardiovascular and respiratory systems in 143 exposed workers. Symptoms were stated to develop more rapidly in female workers than male workers. Also, effects on the function of the central nervous system were reported by Kasimova (1978), and this may be associated with altered cerebral circulation reported in an earlier study (Kasimova, 1977a). Kasimova (1977b) stated that the nervous system damage was related to increasing lengths of exposure to 3-chloropropene. Kasimova (1977c) also observed an exposure-related impairment of thermoregulation in workers exposed to 3-chloropropene for 5 years or more. Although it is difficult to evaluate these studies individually, the studies do lend support to the observation of liver and kidney damage described above in humans and the neurological effects described below in studies in experimental animals. In all of these Russian studies there was no indication of exposure levels.

The only other investigation of the human exposure effects to 3-chloropropene was a limited study of effects on heme synthesis as measured by increased porphyrin excretion in the urine of exposed workers (Nagelsmit et al., 1979). Morning urine was collected and analyzed from a group of 61 workers, 44 of whom were sampled twice. Urine from office workers served as a control. Considerable variation existed between the porphyrin levels in the group tested twice, and, when compared with control values, there was no statistically significant difference. Although exposure data were not given, the authors concluded that porphyrin levels in the urine could not be used to monitor worker exposure to 3-chloropropene.

Chronic animal inhalation studies by Torkelson et al. (1959) support the evidence for kidney and liver damage observed in humans (Table 5-1). In a pilot study, 5 rats of each sex, 4 male guinea pigs and 1 female rabbit were exposed to 8 ppm of 3-chloropropene 7 hours/day, 5 days/week for 7 weeks.

TABLE 6-1

Acute Lethal Effects of 3-Chloropropene to Freshwater Fish

Species	Duration	Concentration (mg/ℓ)	Method	Effect[a]	Reference
Fathead minnow,	24-hour	24.00	static[b]	TL_m	Pickering and Henderson, 1966
Pimephales promelas[b]	24-hour	25.86	static[c]	TL_m	Pickering and Henderson, 1966
	48-hour	24.00	static[b]	TL_m	Pickering and Henderson, 1966
	48-hour	24.00	static[c]	TL_m	Pickering and Henderson, 1966
	96-hour	19.78	static[b]	TL_m	Pickering and Henderson, 1966
	96-hour	24.00	static[c]	TL_m	Pickering and Henderson, 1966
Bluegill sunfish,	24-hour	59.30	static[b]	TL_m	Pickering and Henderson, 1966
Lepomis macrochirus	48-hour	42.33	static[b]	TL_m	Pickering and Henderson, 1966
	96-hour	42.33	static[b]	TL_m	Pickering and Henderson, 1966
Guppies,	24-hour	57.68	static[b]	TL_m	Pickering and Henderson, 1966
Lebistes reticulatus	48-hour	53.54	static[b]	TL_m	Pickering and Henderson, 1966
	96-hour	51.08	static[b]	TL_m	Pickering and Henderson, 1966
Goldfish,	24-hour	26.56	static[b]	TL_m	Pickering and Henderson, 1966
Carrassius auratus	24-hour	<500	static	TL_m	Bridie et al., 1979
	48-hour	20.87	static[b]	TL_m	Pickering and Henderson, 1966
	96-hour	20.87	static[b]	TL_m	Pickering and Henderson, 1966

[a] $TL_m = LC_{50}$

[b] Soft water; pH = 7.5, alkalinity = 18 mg/ℓ, hardness (EDTA) = 20 mg/ℓ

[c] Hard water; pH = 8.2, alkalinity = 300 mg/ℓ, hardness (EDTA) = 360 mg/ℓ

Gross signs of toxicity were not observed, as indicated by decreased body weight or changes in organ weight, although a slight decrease in spleen weight did occur in female rats. Histologic examination revealed marked changes in the liver and kidneys of all animals. Changes in the liver included dilation of the sinusoids, cloudy swelling and focal necrosis, and in the kidneys changes were noted in the glomeruli and in the epithelium of the convoluted tubules (necrosis). In a longer study of 180-199 days, 24 rats, 3 rabbits, 9 guinea pigs and 1 dog of each sex were exposed to 3 ppm of 3-chloropropene for 7 hours/day, 5 days/week. The only adverse effect of treatment reported was a "slight change in the liver of female rats killed immediately after exposure" consisting of central lobular degeneration. This was not observed in animals allowed to recover for a period of 2 months.

Aznaurian et al. (1981) exposed five groups of white rats to 100 mg/m^3 of chloroprene (~20 rats/group) for 4 hours/day for 5 months. At 3.5 months, four groups of rats were fed isocaloric rations with different protein imbalances. In addition, two of these latter groups were adminstered methionine or glutamic acid at 25 or 20 mg/kg bw/day for 13 days. The authors stated that the treatment with chloroprene resulted in serious disturbances in amino acid metabolism, specifically in the biosynthesis of protein. The authors support their claim by stating that the spectrum of free amino acids in various organs and tissues changed and that the rate of amino acid uptake into tissue proteins as well as other proteins decreased. No experimental data were shown.

Neurotoxicity was observed in TO mice treated with 3-chloropropene by gastric intubation for 2-17 weeks (He et al., 1981). Groups of 4-12 animals of each sex received 3-chloropropene at 3 doses weekly of either 300 or 500 mg/kg. The high dose animals were exposed for no more than 70 days, while

the low dose animals were exposed for no more than 120 days. Functionally, treated mice had poor balance and weakness in the limbs, as indicated by the inability to grasp with the hind limbs and by a sprawling gait. Electron microscopic examination revealed degeneration of peripheral nerves and nerves in the spinal column. In addition to the neurological damage, it was reported that 70% of the treated animals developed focal kidney damage.

A chronic oral bioassay was conducted by the NCI (1978) for the purpose of qualitatively determining the potential carcinogenicity of 3-chloropropene. The experimental design has already been discussed (see Section 5.1.). Dose-related increases in acceleration of mortality were observed in rats and mice of both sexes according to the Tarone test when compared to controls. Mean body weights were decreased at both doses in both sexes of rats and in female mice relative to controls. Hunched appearance and abdominal urine stains were noted at earlier times in dosed versus control rats of both sexes. Loss of equilibrium was noted in 8 of 10 high dosed male mice with abdominal distention in all 10. No other toxic signs were reported.

McKenna et al. (1978) reported the results of a study with male and female Sprague-Dawley rats, Golden Syrian hamsters and male beagle dogs (number of animals not given) that were exposed to 0, 3, 10 or 25 ppm of 1,2,3-trichloropropene vapor for 6 hours/day, 5 days/week for a total of 65-67 weeks. Effects of exposure included decreased body weight (rats and male hamsters), elevated SGPT activity (rats) and decreased liver cell size (male hamsters) in animals exposed at the 25 ppm level. General irritation was observed at 25 ppm, while dogs also showed signs of eye irritation at the 10 ppm level. Although non-protein sulfhydryl content in the liver of rats and hamsters decreased following a single exposure, levels had

recovered by the end of the subchronic exposure. Possible participation of glutathione in the detoxification of 1,2,3-trichloropropene was suggested.

Other pertinent data regarding the chronic toxicity of these and other chloropropenes were not located in the available literature.

5.6. ACUTE TOXICITY

An acute oral LD_{50} value of 0.7 g/kg for 3-chloropropene was determined using groups of 6 Sherman rats (Smyth and Carpenter, 1948). The LD_{50} determined from skin absorption in rabbits was 2.2 mℓ/kg, while inhalation exposure for 4 hours to 3-chloropropene at 2000 ppm resulted in one death in the group of six rats. Shamilov and Abasov (1973) reported LC_{50} values of 1900 and 2370 ppm for mice and rats, respectively, following a 2- or 4-hour exposure.

In a more detailed investigation of the inhalation toxicity of 3-chloropropene, Adams et al. (1940) exposed groups of 4 or 5 rats and guinea pigs to the vapors of 3-chloropropene. Exposure to 29,300 ppm for 0.5 hours resulted in 100% death in rats, while 100% of the animals survived exposure for 0.25 hours. At the lowest level tested, 290 ppm, rats and guinea pigs survived 3- and 1-hour exposures, but did not survive an 8- and 4-hour exposure, respectively. Gross signs of exposure were irritation and narcosis, and death occurred soon after loss of consciousness. Histologic examination revealed kidney damage after longer, low level exposures and lung damage with short, high level exposures. The kidney damage included hemorrhage, congestion and damage to the convoluted tubules. The lungs showed typical congestion and hemorrhage associated with exposure to irritant vapors. The gross and histologic signs of toxicity were qualitatively the same for both rats and guinea pigs, but the guinea pig was more sensitive to 3-chloropropene.

Smyth et al. (1962) also determined the LD_{50} value for 1,2,3-trichloropropene following oral administration to rats or dermal application to rabbits. The values were 0.62 g/kg and 0.64 mℓ/kg, respectively. Five of a group of six rats died following inhalation exposure for 4 hours to 500 ppm of 1,2,3-trichloropropene. Fedyanina et al. (1975) reported oral LD_{50} values for 1,2,3-trichloropropene of 0.25, 0.345 and 0.381 g/kg for mice, rats and rabbits, respectively, while the inhalation LC_{50} for mice was 2.8 mg/ℓ for a 2-hour exposure.

In a similar range-finding study, Smyth et al. (1969) examined the acute toxicity of 1,1,2,3-tetrachloropropene. In this study, the oral LD_{50} was 0.35 mℓ/kg in rats and the dermal LD_{50} in rabbits was 0.40 mℓ/kg. Five of six rats died following inhalation exposure for 4 hours to 250 ppm of 1,1,2,3-tetrachloropropene. Oral LD_{50} values reported by Fedyanina et al. (1975) for 1,1,2,3-tetrachloropropene were 0.8, 1.07 and 0.477 g/kg for mice, rats and rabbits, respectively, and an LC_{50} value of 3.2 mg/ℓ was determined in mice.

5.7. OTHER RELEVANT INFORMATION

Torkelsen et al. (1959) had 13 human volunteers attempt to identify 3-chloropropene in the atmosphere at a level of 3 ppm. Following a 1- to 3-minute exposure, 10 subjects observed an odor, but none reported any irritation. It was concluded that sensory perception of 3-chloropropene provided little warning of the presence of this compound near the level of 8 ppm determined to be toxic in experimental animals.

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

Acute mortality tests for 3-chloropropene have been conducted with four species of freshwater fish (Pickering and Henderson, 1966). As summarized in Table 6-1, fathead minnows were more sensitive to 3-chloropropene than bluegills or guppies, but were not more sensitive than goldfish. The 96-hour LC_{50} values appeared in general to be slightly lower than the 24-hour values. Water hardness was found to have no significant effect on the toxicity of the chemical to fathead minnows.

Cell multiplication of protozoans, Entosiphon sulcatum Stein (bacteriovorous flagellate) and Uronema parduczi Chatton-Lwoff (bacteriovorous ciliate), was inhibited by exposure to 3-chloropropene at concentrations of 8.4 mg/ℓ (72 hours) and >240 mg/ℓ (20 hours), respectively (Bringmann and Kuehn, 1980b).

Information on the acute toxicity of the other, more highly chlorinated propenes being reviewed was unavailable. Some data were available, however, on the acute effects of 1,3-dichloropropene, which is used as a nematocide (Johnson and Finley, 1980). In a 96-hour static test, 1,3-dichloropropene was more toxic to fathead minnows than 3-chloropropene with an LC_{50} of 4.1 mg/ℓ. Values for other species tested with 1,3-dichloropropene were 3.65 mg/ℓ for largemough bass and 1.08 mg/ℓ for walleye. A 48-hour LC_{50} of 0.09 mg/ℓ was found Daphnia magna (Johnson and Finley, 1980).

6.2. CHRONIC EFFECTS

Pertinent data regarding chronic effects of the chloropropenes on aquatic organisms were not located in the available literature.

TABLE 5-1

Hazard Assessment Table for Inhalation Toxicity[a]

Species, Strain	Sex	No. at Start	Physical State	Purity	Exposure	(l_e)[b]	(L_e)[c]	Response
Rat	M F	5 5	vapor	high purity	8 ppm 7 hrs/day, 5 days/week	35 days	36 days	No change in body weight. On histologic examination, all animals had kidney and liver damage including necrosis.
Guinea pig	M	4						
Rabbit	F	1						
Rats	M F	24 24	vapor	high purity	3 ppm 7 hrs/day, 5 days/week	80-194 days	180-194 days	Only observed effect was a slight degeneration in the central lobular portion of the liver in female rats. Damage was no longer present if animals were allowed to recover for 2 months.
Guinea pigs	M F	9 9						
Rabbits	M F	3 3						
Dogs	M F	1 1						

[a]Source: Torkelson et al., 1959

[b]Duration of exposure

[c]Duration of experiment

6.3. PLANT EFFECTS

Bringmann and Kuehn (1978, 1980a) determined that cell multiplication of Microcystis aeruginosa (blue-green alga) and Scenedesmus quadricauda (green alga) was inhibited by exposure to 8.2 and 6.3 mg/ℓ 3-chloropropene, respectively, for 8 days.

6.4. RESIDUE

Experimental data regarding chloropropene residues in aquatic organisms were not located in the available literature. Veith et al. (1980) have suggested, however, the use of the following equation to estimate BCF:

$$\log BCF = 0.76 \log K_{ow} - 0.23$$

where K_{ow} is the octanol-water partition coefficient. Using this equation and the log K_{ow} reported by Mabey et al. (1982) for 1,2,3-trichloropropene (2.07), the BCF for whole fish was calculated to be ~3. Therefore, significant bioconcentration of this compound is not expected.

6.5. OTHER RELEVANT INFORMATION

Bringmann and Kuehn (1980a) determined that multiplication of the bacterium Pseudomonas putida was inhibited by exposure to 115 mg/ℓ 3-chloropropene for 16 hours.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Of the chloropropenes reviewed here, guidelines exist only for 3-chloropropene. The American Conference of Governmental Industrial Hygienists (ACGIH, 1980) recommends an 8-hour threshold limit value (TLV) of 1 ppm, and a short-term exposure limit (STEL) of 2 ppm. NIOSH (1976) has recommended a ceiling limit of 3 ppm for any 15-minute period. 3-Chloropropene is also regulated by the U.S. Department of Labor, Occupational Safety and Health Administration (29 CFR 1910.1000, Table Z). The current standard for this compound is 1 ppm (3 mg/m^3) for an 8-hour work shift.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of the four chloropropenes have not been derived.

8. APPROACHES TO RISK ASSESSMENT

There is insufficient toxicologic information available to support derivation of an acceptable daily intake (ADI) for 1,1,2,3-tetrachloropropene or 1,1,2,3,3-pentachloropropenes. There are, however, limited experimental and human data with 3-chloropropene and 1,2,3-trichloropropene, that taken together, are sufficient to derive ADIs. The ACGIH (1980) TLV for 3-chloropropene of 1 ppm is based on the two subchronic studies by Torkelson et al. (1959) in which a number of species of experimental animals were exposed to 8 or 3 ppm for ~1 and 6 months, respectively. The 3 ppm level was a no observed adverse effect level (NOAEL) as indicated by slight but reversible liver alteration in female rats. An NCI (1978) bioassay is also available from which an ADI might be calculated. This bioassay, however, did not fully attribute the adverse effects described to particular doses. Furthermore, a significant acceleration of mortality was observed in rats of both sexes, indicating that the doses used might be considered Frank Effect Levels (FELs). According to present methodology (45 FR 79353, 1980) such effect levels cannot be used to estimate ADIs because there is no assurance that they are in the proximity of a threshold region.

Using the TLV of 1 ppm (3 mg/m^3) and a safety factor of 100, the ADI for humans of 3-chloropropene can be calculated to be 1.5 µg/kg as follows:

$$ADI = \frac{3\ mg/m^3 \times 10\ m^3 \times 5/7 \times 0.5}{100 \times 70\ kg}$$

$$= 0.0015\ mg/kg \text{ or } 1.5\ \mu g/kg.$$

This value is equivalent to 0.11 mg/day for a 70 kg person. In this calculation it was assumed that a human breathes 10 m^3 of air in a work day, and that in the absence of other information the absorption coefficient for 3-chloropropene was 0.5. The exposure was also extended from a 5-day work week to a 7-day week. The safety factor of 100 was chosen to reflect a

10-fold factor to account for sensitive individuals and a 10-fold factor since the TLV of 1 ppm was relatively close to the FEL of 8 ppm reported by Torkelson et al. (1959) for a 1-month exposure of laboratory animals. Also, there is some suggestive evidence that 3-chloropropene is mutagenic (although the data base should be broadened to include other mutagenesis bioassays), and a NCI (1978) bioassay suggests a slight carcinogenic potential for this compound. Until more definitive evidence is available on the toxicity, mutagenicity and carcinogenicity of 3-chloropropene, it would be prudent to use a safety factor of 100.

An ADI for 1,2,3-trichloropropene can be derived from the inhalation studies on rats, hamsters and dogs by McKenna et al., 1978. This study was of 65-67 weeks duration; doses of 3, 10 or 25 ppm of 1,2,3-trichloropropene were administered 6 hours/day 5 days/week. Eye irritation was observed at 10 ppm in dogs but not at 3 ppm. Therefore, 3 ppm was selected as a basis for the ADI. [According to methodology (45 FR 79353, 1980) the highest NOEL or NOAEL is used as a basis for ADI calculations when available.] A human was assumed to breath 20 m^3 of air/day. Trichloropropene has a molecular weight of 145.4. Thus, 1 ppm = 5.96 mg/m^3 and 3 ppm = 17.9 mg/m^3.

$$ADI = \frac{17.9\ mg/m^3 \times 20\ m^3 \times 5/7 \times 6/24 \times 0.5}{100 \times 70}$$

$$= 0.00456\ mg/kg/day$$

$$= 0.32\ mg/day\ for\ a\ 70\ kg\ man$$

The uncertainty factor of 100 represents 10-fold for interspecies variability and 10-fold for intraspecies variability to the toxicity of said chemical. In the absence of specific data a retention factor of 0.5 was assumed.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air, 4th ed., Cincinnati, OH. p. 12.

Adams, E.M., H.C. Spencer and D.D. Tensh. 1940. The acute vapor toxicity of allyl chloride. J. Ind. Hyg. Toxicol. 22: 79-86.

Alekperov, I.I., S.B. Shirinova and V.V. Lagunova. 1980. Functional state of the liver in workers in allyl chloride production. J. Vrach. Delo. (6): 111-113. (Rus.)

Aleskerov, F.A. 1979a. Status of the respiratory and cardiovascular system in workers engaged in allyl chloride production. J. Azerb. Med. Zh. 56(4): 48-52. (Rus.)

Aleskerov, F.A. 1979b. Phase structure of left-ventricular systole in workers involved in allyl chloride production. J. Azerb. Med. Zh. 56(7): 54-57. (Rus.)

Aleskerov, F.A. 1977. Status of the external respiration function in workers coming in contact with allyl chloride. J. Tr. Azerb. 11: 77-81. (Rus.)

Ali-Zade, G.A. 1979. Functional state of kidneys in workers exposed to some chemical substances (allyl chloride, metallic mercury). J. Gig. Tr. Prof. Zabol. (10): 22-25. (Rus.)

Aznaurian, A.V., M.P. Erznkatian and A.S. Aznaurian. 1981. Some pathomorphological changes in the organs of rats in chronic chloroprene poisoning against the background of use of rations with different concentrations of protein. Zh. Eksp. Klin. Med. 21: 136-140.

Bignami, M., G. Conti, L. Conti, et al. 1980. Mutagenicity of halogenated aliphatic hydrocarbons in Salmonella typhimurium, Streptomyces coelicolor and Aspergillus nidulans. J. Chem. Biol. Interact. 30(1): 9-23.

Biles, R.W., T.H. Conner, N.M. Trieff and M.S. Legator. 1978. The influence of contaminants on the mutagenic activity of dibromochloropropane (DBCP). J. Environ. Pathol. and Toxicol. 2: 301-312.

Bridie, A.L., C.J.M. Wolff and M. Winter. 1979. BOD and COD of some petrochemicals. Water Res. 13: 627-630.

Briggs, G.C. 1981. Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors and the parachor. J. Agric. Food Chem. 29: 1050-1059.

Bringmann, G. and R. Kuehn. 1980a. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14(3): 231-241.

Bringmann, G. and R. Kuehn. 1980b. Determination of the biological effect of water pollutants in protozoa. II. Bacteriovorous ciliates. Z. Wasser Abwasser Forsch. 13: 26-31. (Ger.)

Bringmann, G. and R. Kuehn. 1978. Testing of substances for their toxicity threshold: Model organisms Microcystis (Diplocystis) aeruginosa and Scenedesmus quadricauda. Mitt. Internat. Verein Limnol. 21: 275-284. (Ger.)

Brown, S.L., F.Y. Chan, J.L. Jones, et al. 1975. Research program on hazard priority ranking of manufactured chemicals, phase II -- Final report. Prepared by SRI International for National Science Foundation, Washington, DC. NTIS PB263164.

Burns, L.H., B.M. Cline and R.R. Lassiter. 1981. Exposure Analysis Modeling System (EXAMS). Prepared by Environmental Research Lab, Office of Research and Development, U.S. EPA, Athens, GA.

Callahan, M.A., M.W. Simak, N.w. Gabel, I.P. May and C.F. Fowler. 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Vol. 2, U.S. EPA 440/4-79-029b, Office of Water Planning and Standards, Office of Water and Waste Management, U.S. EPA, Washington, DC. PB 80-204381.

CPAR (Cooperative Pollution Abatement Research Programme). 1978. CPAR Project Report 678-1: Biological Characteristics of Pulp Mill Effluents, Part I. Prepared by B.C. Research, Vancouver, B.C. Prepared for CPAR Secretarial, Environmental Protection Service, Environment Canada, Ottowa, Ontario.

De Lorenzo, F., S. Degl'Innocenti, A. Ruocco, R. Silengo and R. Cortese. 1977. Mutagenicity of pesticides containing 1,3-dichloropropene. J. Cancer Res. 37: 1915-1917.

Dilling, W.L. 1977. Interphase transfer processes. III: Evaporation rates of chloromethane, ethanes, ethylenes, propanes, and propylenes from dilute aqueous solutions. Comparison with theoretical predictions. J. Environ. Sci. Technol. 11: 405-409.

Dilling, W.L., N.B. Teferhiller and G.J. Kallas. 1975. Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other chlorinated compounds in dilute aqueous solutions. J. Environ. Sci. Technol. 9: 833-838.

Eder, E., T. Neudecker, D. Lutz and D. Henschler. 1980. Mutagenic potential of allyl and allylic compounds: Structure-activity relationship as determined by alkylating and direct in vitro mutagenic properties. J. Biochem. Pharmacol. 29(7): 993-998.

Ellenton, J.A., G.R. Douglas and E.R. Nestmann. 1981. Mutagenic evaluation of 1,1,2,3-tetrachloro-2-propene, a contaminant in pulp mill effluents, using a battery of in vitro mammalian and microbial tests. Can. J. Genet. Cytol. 23(1): 17-25.

Fedyanina, V.N., B.Ya. Ekshtat, M.N. Pavlenko and S.S. Kazanina. 1975. Toxicity of trichloropropene and tetrachloropropene. J. Uch. Zap. 22: 53-58. (Rus.)

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl 4): 66-75.

Hausler, M. and R. Lenich. 1968. Effect of chronic occupational allyl chloride exposure. Arch. Toxicol. (Berl) 23: 209-214. (Cited in NIOSH, 1976)

Hawley, G.G., Ed. 1971. Condensed Chemical Dictionary. Van Nostrand Rheinhold Books, NY.

He, F., J.M. Jacobs and F. Scaravilli. 1981. The pathology of allyl chloride neurotoxicity in mice. Acta Neuropathol. 55(2): 125-133.

Ivanetich, K.M., S. Lucas, J.A. Marsh, M.R. Ziman, I.D. Katz and J.J. Bradshaw. 1978. Organic compounds: Their interaction with and degradation of hepatic microsomal drug-metabolizing enzymes in vitro. J. Drug Metab. Dispos. 6(3): 218-225.

John, J.A., M.M. Deacon, J.A. Ayres and J.F. Quast. 1980. Teratologic Evaluation of Allyl Chloride in Laboratory Animals: 20th Annual Meeting of the Teratology Society, Portsmouth, NH, June 8-12. Teratology. 21(2):47A.

Johnson, W.W. and M.T. Finley. 1980. Handbook of acute toxicity of chemicals to fish and aquatic invertebrates. Fish and Wildlife Service, Resource Publication 137, Washington, DC.

Kasimova, F.S. 1978. Early functional changes in the central nervous system of workers engaged in the manufacture of allyl chloride. J. Gig. Tr. Prof. Zabol. (4): 24-27. (Rus.)

Kasimova, F.S. 1977a. Rheographic study of the state of cerebral circulation in people employed in allyl chloride production. J. Gig. Tr. Prof. Zabol. (10): 48-49. (Rus.)

Kasimova, F.S. 1977b. Effect of allyl chloride on the functional state of the central nervous system. J. Azerb. Med. Zh. 54(3): 56-60. (Russ.)

Kasimova, F.S. 1977c. Evaluation of the state of thermoregulation in workers of the allyl chloride industry. J. Azerb. Med. Zh. 54(5): 43-45. (Rus.)

Kaye, C.M., J.J. Clapp and L. Young. 1972. Metabolic formation of mercapturic acids from allyl halides. Xenobiotica. 2(2): 129-139.

Kenaga, E.E. and C.A.I. Goring. 1980. Relationship between water solubility, soil sorption, octanol-water partitioning and concentration of chemicals in biota. In: Aquatic Toxicology, ASTM STP 707, J.G. Eaton, P.R. Parrish and A.C. Hendricks, Ed. Am. Soc. Test. Mater. Philadelphia, PA. p. 78-115.

Kiparisova, L.S. and V.E. Stepanenko. 1976. Gas-chromatographic determination of some chlorinated hydrocarbons in the air of industrial installation. Gig. Sanit. 6: 54-55. (Rus.)

Mabey, W. and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7: 383-415.

Mabey, W.R., H. Jaber, J. Winterle, et al. 1982. Estimates of data for chemicals on the list "Constituents of concern for chlorinated organic listings". EPA Contract No. 63-03-2981. OHEA, U.S. EPA, Washington, DC.

McCoy, E.C., L. Burrows and H.S. Rosenkranz. 1978. Genetic activity of allyl chloride. Mutat. Res. 57: 11-15.

McKenna, M.J., J.F. Qusat and G.A. Stevens. 1978. Results of a 90 day inhalation toxicity study of 1,2,3-trichloropropene in laboratory animals. Toxicol. Appl. Pharmacol. 45(1): 249.

Melnikov, N.N. 1971. IV. Halogen derivitives of aliphatic hydrocarbons. In: Residue Reviews, Vol. 36, F.A. Gunther and J.D. Gunther, Ed. Springer-Verlag, NY. p. 35-36.

Nagelsmit, A., P.W. Van Vliet, W.A.M. Van der Wiel-Wetzels, et al. 1979. Porphyrins as Possible Parameters for Exposure to Hexachlorocyclopentadiene, Allylchloride, Epichlorohydrin and Endrin. In: Chemical Porphyria in Man. J.J. Strik and J.H. Koeman, Ed. Elsevier/North-Holland Biomedical Press, Amsterdam, Netherlands. p. 55-61.

NCI (National Cancer Institute). 1978. Bioassay of Allyl Chloride for Possible Carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 73. [Also Publ. as DHHS (NIH) 78-1323.]

Nestmann, E.R., E.G. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79(3): 203-212.

Neudecker, T., D. Lutz, E. Eder and D. Henschler. 1980. Structure-activity relationship in halogen- and alykl-substituted allyl and allylic compounds: Correlation of alkylating and mutagenic properties. J. Biochem. Pharmacol. 29(19): 2611-2617.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard...Occupational Exposure to Allyl Chloride. U.S. DHEW, GPO, Washington, DC. Publ. No. 76-204.

Patel, J.M., E. Ortiz and K.C. Leibman. 1981. Destruction of hepatic cytochrome P-450 by allylic industrial toxicants. 65th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlanta, GA. April 12-17. Fed. Proc. 40(3 Part 1): 636.

Torkelson, T.R. and V.K. Rowe. 1981. Halogenated Aliphatic Hydrocarbons Containing Chloride, Bromine and Iodine. In: Patty's Industrial Hygiene and Toxicology. Vol. 2B, 3rd rev. ed., G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 3568-3573.

Pellizzari, E.D., J.E. Bunch, R.E. Berkley and J. McRae. 1976. Determination of trace hazardous organic vapor pollutants in ambient atmospheres by gas chromatography/mass spectrometry/computer. Anal. Chem. 48: 803-807.

Pickering, Q.H. and C. Henderson. 1966. Acute toxicity of some important petrochemicals to fish. J. Water Pollut. Control Fed. 38(9): 1419-1429.

Schwarzenbach, R.P. and J. Westall. 1981. Transport of nonpolar organic compounds from surface water to groundwater laboratory sorption studies. Environ. Sci. Technol. 15: 1360-1367.

Sears, T. 1973. Photochemistry of allyl chloride in the gas-phase. Ph.D. dissertation. University of California, Davis. Ann Arbor, MI.

Shamilov, T.A. and D.M. Abasov. 1973. Effect of allyl chloride on animals under experimental conditions. J. Tr. Azerb. Nauchno-Issled. Inst. Gig. Tr. Prof. Zabol. 8: 12-15. (Rus.)

Simmon, V.F. 1978. Structural correlations of carcinogenic and mutagenic alkyl halides. DHEW Publ. FDA 78-1046. p. 163-171.

Smyth, H.F. and C.P. Carpenter. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. p. 30, 63, 48.

Smyth, H.F., Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani and B.S. Striegel. 1962. Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. p. 23, 95, 62.

Smyth, H.F., Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J.A. Striegel and J.S. Nycum. 1969. Range-finding toxicity data: VII. Am. Ind. Hyg. Assoc. J. 30(5): 470-476.

SRI (Standford Research Institute). 1981. Directory of Chemical Producers, United States of America. SRI International, Menlo Park, CA.

Stolzenberg, S.J. and C.H. Hine. 1980. Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. Environ. Mutagen. 2(1): 59-66.

Theiss, J.C., M.B. Shimkin and L.A. Poirier. 1979. Induction of pulmonary adenomas in strain A mice by substituted organohalides. J. Cancer Res. 39(2): 391-395.

Torkelson, T.R., M.A. Wolf, F. Oyen and V.K. Rowe. 1959. Vapor toxicity of allyl chloride as determined on laboratory animals. Am. Ind. Hyg. Assoc. J. 20: 217-223.

Van Duuren, B.L., B.M. Goldschmidt, G. Lowengart, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63(6): 1433-1440.

Veith, G.D., K.J. Macek, S.R. Petrocelli and J. Carroll. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. In: Aquatic Toxicology, ASTM STP 707, J.G. Eaton, P.R. Parrish and A.C. Hendricks, Eds. Am. Soc. Test. Mater. p. 116-129.

Weast, R.C., Ed. 1980. CRC Handbook of Chemistry and Physics. CRC Press, Boca Raton, FL. p. c-523.

Weisburger, E.K. 1977. Carcinogenicity studies on halogenated hydrocarbons. J. Environ. Health Perspect. 21: 7-16.